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Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire
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# COMMUNICATION

The European Patent Office herewith transmits as an enclosure the European search report for the above-mentioned European patent application.

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# EUROPEAN SEARCH REPORT

Application Number
EP 01 30 2779

## DOCUMENTS CONSIDERED TO BE RELEVANT

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The present search report has been drawn up for all claims

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| MUNICH | 4 December 2001 | Barba, M |

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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# ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 01 30 2779

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| C07D 237/22, A61K 31/50 | A1 | (43) International Publication Date: 23 July 1992 (23.07.92) |

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**Published**
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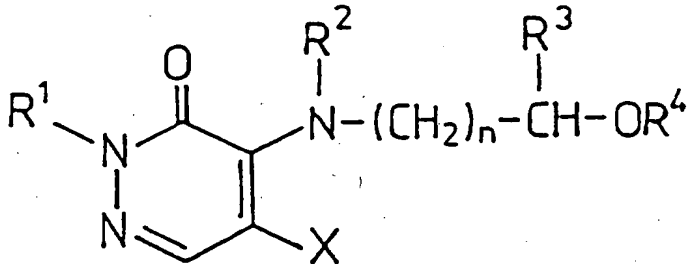
(54) Title: NOVEL 3(2H)-PYRIDAZINONES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND PROCESS FOR PREPARING SAME



(I)

(57) Abstract

The invention relates to novel, racemic and optically active 3(2H)-pyridazinone derivatives of general formula (I), wherein $R^1$ means hydrogen; a $C_{1-4}$alkyl group optionally substituted by an $R^5R^6N$- group where $R^5$ and $R^6$, being the same or different, stand for a $C_{1-4}$alkyl group or $R^5R^6N$- together represents a 6-membered heterocyclic group optionally containing an oxygen or an $R^7N$- moiety where $R^7$ is a $C_{1-4}$alkyl optionally substituted by a phenyoxy group or a $C_{3-5}$alkenyl optionally substituted by a phenyl group; or a $C_{1-4}$alkyl group substituted by a mono- or polysubstituted phenyl, phenoxy or benzyloxy group; or a $C_{3-5}$alkenyl or $C_{3-5}$alkynyl optionally substituted by an unsubstituted or optionally substituted phenyl group; or a phenyl group; $R^2$ means hydrogen; or a $C_{1-4}$alkyl optionally substituted by a morpholino, pyridyl, 1,4-benzodioxanyl or an optionally substituted phenyl group; $R^3$ means hydrogen or an optionally substituted phenyl group; $R^4$ means hydrogen; or $R^8CO$- group where $R^8$ is a $C_{1-4}$alkyl, phenyl or pyridyl group or an amino group substituted by a $C_{1-4}$alkyl group; or an $-SO_3M$ moiety where M is hydrogen or an organic or inorganic cation; X means halogen; and n is 1, 2 or 3, with the proviso that $R^1$ is different from a $C_{1-4}$alkyl, alkenyl, aralkyl and phenyl group when n is 1, as well as their tautomers and the acid addition salts of these compounds. The invention further relates to pharmaceutical compositions containing as active ingredient a compound of general formula (I) as well as to a process for the preparation of compounds of general formula (I). The comp unds of the invention possess a significant calmodulin-antagonizing effect, decrease the coronary resistance and are less toxic. Thus, these compounds are useful for treating cardiovascular diseases, particularly angina pectoris.

BNSDOCID: <WO___9212137A1_I_>

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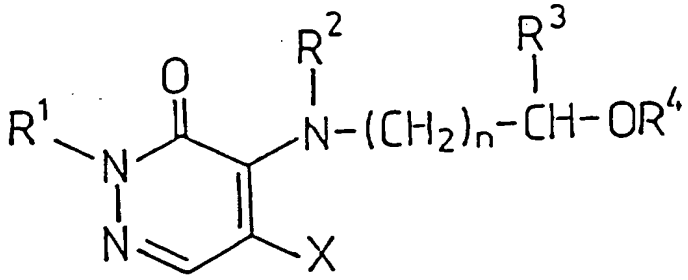
# NOVEL 3(2H)-PYRIDAZIN NES, PHARMACUTICAL COMPOSITIONS CONTAINING THEM AND PROCESS FOR PREPARING SAME

This invention relates to novel 3(2H)-pyridazinones of the general formula (I),



(I)

wherein

$R^1$ means hydrogen; a $C_{1-4}$alkyl group optionally substituted by an $R^5R^6N$- group where $R^5$ and $R^6$, being the same or different, stand for a $C_{1-4}$alkyl group or $R^5R^6N$- together represents a 6-membered heterocyclic group optionally containing an oxygen or an $R^7N$- moi ty where $R^7$ is a $C_{1-4}$alkyl optionally substituted by a phenyoxy group or a $C_{3-5}$alkenyl optionally substitut d by a phenyl grup; or a $C_{1-4}$alkyl group substituted by a mono- or polysubstituted phenyl, phenoxy or benzyloxy group; or a $C_{3-5}$alkenyl or $C_{3-5}$alkynyl optionally substituted by an unsubstituted or optionally substituted phenyl group; or a phenyl group;

$R^2$ stands for: hydrogen; or a $C_{1-4}$alkyl optionally substitut d by a morpholino, pyridyl, 1,4-benzodioxanyl

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or an optionally substituted phenyl group;

$R^3$ m ans hydrogen or an optionally substituted phenyl group;

$R^4$ means hydrogen; or $R^8CO$- group where $R^8$ is a $C_{1-4}$alkyl, phenyl or pyridyl group or an amino group substitut d by a $C_{1-4}$alkyl group; or an $-SO_3M$ moiety where M is hydrogen or an organic or inorganic cation;

X means halogen; and

n is 1, 2 or 3,

with the proviso that $R^1$ is different from a $C_{1-4}$alkyl, alkenyl, aralkyl and phenyl group when n is 1,

as well as their tautomers, racemic and optically opti nally active forms, mixtures thereof and acid addition salts of these compounds as well as pharmaceutical compositions containing these compounds.

According to an other aspect of the invention, there is provided a process for the preparation of the new compounds of general formula (I).

The compounds according to the invention are endowed with valuable therapeutical, chiefly cardiovascular, particularly antianginal properties and have also a significant calmodulin-antagonizing effect.

A particularly preferred group of the compounds according to the invention are compounds of the general formula (I), wherein: $R^1$ means a $C_{3-5}$alkenyl group substituted by an optionally substituted phenyl group; $R^2$ stands for a benzyl or 1,4-benzodioxanylmethyl group; $R^3$ is hydrogen or methoxy-substituted phenyl group; $R^4$ repr sents

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hydrogen or pyridylcarbonyl group; X means chlorine or bromine; and n is 1, 2 or 3.

An other preferable group of the invention contains compounds of the general formula (I), wherein $R^1$ stands for a $C_{1-4}$alkyl group optionally substituted by an $R^5R^6N$- group where $R^5$ and $R^6$ are as defined above, or by a methoxy-substituted phenyl or benzyloxy group; $R^2$ means benzyl group; $R^3$ is hydrogen; $R^4$ stands for hydrogen or an $-SO_3M$ group wher M is as defined above; X represents chlorine; and n is 1, 2 or 3.

The novel 4-(substituted amino)-3(2H)-pyridazinones are the members of a compound class, which has relatively less been studied up to the present.

The Japanese patent specification (published patent application) No. 78-12880 relates to 2-alkyl, 2-alkenyl, 2--aralkyl and 2-aryl derivatives of structurally related 5- and 4-[(2-hydroxyethyl)amino]-3(2H)-pyridazinone compounds, which are the intermediates of antiinflammatory, analgetic and antidepressive pyridazino[3,4-b][1,4]oxazine derivatives.

The Czechoslovakian patent specification No. 223,432 discloses 2-$C_{1-3}$alkyl-, 2-cycloalkyl-, 2-aryl- and 2-(optionally substituted)aralkyl-5-chloro-3(2H)-pyridazinones containing an alkyl, alkoxyalkyl cycloalkylamino, pyrrolidino or piperidino group in 4-position. These compounds are insecticidally and acaricidally active. The preparation of hydroxyl-substituted alkylamino derivatives does not fall within the scope of this invention. The compounds falling within the scope of the invention ar prepared by r acting

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4,5-dichl ro-3(2H)-pyridazinones with a little excess of th respective (appropriate) amino compound in an inert solvent at an elevated temperature. Essentially the same class of compounds is described in an article of Konecny et al. [Coll. Czech. Chem. Comm. 50, pages 492-502 (1985)]. In this relation, the relative reactivity of the chlorine atoms of 4,5-dichloro-3(2H)-pyridazinones was also investigated: it has been stated that the exchange reaction of the 4-chlorine atom is favourized by using a little excess of the amine and toluene as solvent; whereas the use of a polar protic solv nt promotes the exchange reaction of the 5-chlorine atom, although the isomer ratio depends also upon the substitutents. Though the reaction of the 5-chlorine atom can be made practically predominant by the suitable choice of conditions and the yields are also good, the preparativ yield of the product formed by the substitution of the 4-chlorine atom is usually very low, particularly when a secondary amine is employed as reagent.

It is known that cardiovascular diseases are the leading causes of death in several countries of the world. Angina pectoris, a disease affecting a very wide population also belongs to these disorders. The therapeutically used nitrate compounds, beta-adrenergic blocking agents and calcium channel inhibitors are not in each case effective, even when used in combination; in addition, their use is not rarely restricted or ven contraindicated by their side effects or accompanying dis ases.

The syndrome of angina pectoris occurs, when the actual

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oxygen demand of th myocardium (heart muscle) exceeds the oxygen supply. Due to hypoxia, th disturb d balanc induces the ischaemia of myocardium together with all severe sequels (anaerobic metabolism, chest pain, alteration in the ST segment). The medicinal intervention is aimed at restoration of the balance and elimination (abolishment) of the hypoxic periods (episodes). A usual way of increase in the oxygen supply consists e.g. in the decrease of resistance of th cronary vessels, and switching over of the local regulation of circulation. In spite of the attempts of medicinal therapy since more than hundred years, the medicinal treatment of angina pectoris has not been solved up to the present.

In the cases of nitrates addiction, vertigo, headach and the exacerbation of symptoms at an abrupt deprivation of the drug have mainly to be considered, however, hypotension and bradycardia may also develop.

When using beta-adrenergic blocking agents, disadvantageous effects exerted on the serum lipid level as well as a myocardium infarction eventually occurring at th abrupt deprivation of the drug should be taken in account inter alia.

The most important side effects of the calcium chann l inhibitors are headache, constipation and peripheral edema.

Based on recent results, an antianginal effect can be expected also from calmodulin antagonists, particularly by the recognition that a numb r of "lipophilic calcium antagonists" such as e.g. prenylamine and fendiline have be n proved to poss ss also calmodulin-antagonizing action

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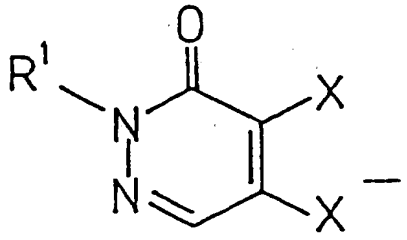
[Mannhold: Drugs of Future 9, pages 677-690 (1984)].

It has surprisingly been found during our investigations that the novel 3(2H)-pyridazinones of the general formula (I), wherein $R^1$, $R^2$, $R^3$, $R^4$, X and n are as defined above, possess an excellent antianginal and calmodulin-antagonistic action without causing any notable side effect.

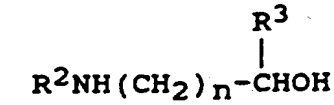
According to the invention the compounds of general formula (I) are prepared by

a) reacting a compound of general formula (II),



(II)

wherein $R^1$ and X are as defined above, with an amine of the general formula (III),



(III)

wherein $R^2$, $R^3$ and n are as defined above,

to obtain compounds of the general formula (I), wherein $R^4$ stands for hydrogen and $R^1$, $R^2$, $R^3$, X and n are as defined above; or

b) treating a compound of the general formula (I), wherein $R^4$ means hydrogen, $R^1$ is as defined above, except hydrogen, and $R^2$, $R^3$, X as well as n are as

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defin d above, with an agent b ing suitabl to intr duce an $R^8CO$- group, wher $R^8$ is as d fined above, to obtain compounds of the general formula (I), wh rein $R^4$ stands for $R^8CO$- group, $R^1$ is as defined above, except hydrogen, and $R^2$, $R^3$, X, n and $R^8$ are as d fined above; or

c) treating a compound of the general formula (I), wh rein $R^4$ means hydrogen, $R^1$ is as defined above, except hydrogen, and $R^2$, $R^3$, X and n are as defined above, with chlorosulfonic acid or with a complex of sulfur trioxide being suitable to introduce the sulfonic acid group, then, if desired, transforming the compound thus obtained to its salt by reacting it with an organic or inorganic base,

to obtain compounds of the general formula (I), wherein $R^4$ represents an $-SO_3M$ group, $R^1$ is as defined above, except hydrogen and $R^2$, $R^3$, X, n and M are as defin d above,

and, if desired, transforming a base of the general formula (I), wherein $R^1$, $R^2$, $R^3$, $R^4$, X and n are as defined abov , obtained by any of the above processes a) to c), to its acid addition salt in a manner known per se and/or, if desired, transforming one of its acid addition salts to an other acid addition salt and/or, if desired, liberating a base of the general formula (I) from its salt.

According to a preferred embodiment of process a) of the invention a 4,5-dihalo-3(2H)-pyridazinone derivativ of the general formula (II) is reacted with a 3- to 10-fold

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molar excess of the amin of g neral formula (III) in a melt state at a temperatur betw n 80 °C and 140 °C. In this case the time of reaction is relatively short and the 4-(hydroxy-alkyl)amino derivative can be separated in a pure form.

According to an other preferred embodiment of proc ss a) of the invention, this reaction is carried out by using a high, suitably 5- to 15-fold, particularly suitably 10-fold molar excess of the amine in an apolar aprotic solvent, preferably in dioxane and/or toluene or in a less polar aprotic solvent, e.g. tertiary, iso- or n-butanol, at a temperature between 50 °C and the boiling point of the reaction mixture, preferably at the boiling point.

An advantageous embodiment of process b) of the invention for the preparation of derivatives containing an alkyl or aryl group as $R^8$ comprises reacting a compound of the general formula (I) containing hydrogen as $R^4$ with a reactive carboxylic acid derivative, preferably the acyl chloride or acid anhydride in an inert solvent in the presence of a tertiary amine base as solvent at a temp rature between 0 °C and 70 °C, preferably between 20 °C and 50 °C. In order to obtain derivatives containing an alkylamino group as $R^8$, a compound of the general formula (I) containing hydrogen as $R^4$ is treated with the appropriate alkyl isocyanate in an inert solvent, preferably benzene or dioxane at a temperature between 20 °C and the boiling point of the reaction mixture.

The process c) according to the inv ntion for preparing derivatives containing an $-SO_3M$ group as $R^4$ can preferably

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b r alized by r acting a compound of th general formula (I) containing hydrog n as $R^4$ with chlorosulfonic acid in an inert solvent, preferably carbon tetrachloride at a temperature between 0 °C and 25 °C. During working up of the reaction mixture, the sulfonic acid obtained is separat d or, if desired, it is transformed in situ to its salt, pr f rably e.g. to its sodium salt.

According to an other preferred embodiment of process c) of the invention a compound of the general formula (I) is treated with a complex of sulfur trioxide, preferably with the complex formed with pyridine, in a suitable solvent, preferably in pyridine thereafter, if desired, the pyridine salt of the sulfonic acid derivative obtained is separated and/or, the sulfonic acid derivative is liberated and, if desired, transformed to an other sulfonic acid salt.

The reaction mixture obtained as a result of the processes discussed above may be worked up by using the usual methods of the organic chemical practice, e.g. by extraction, chromatography and/or crystallization following the removal of the excess of the reagent and/or solvent optionally under reduced pressure. If desired, the resulting compound of the general formula (I) may be purified e.g. by chromatography and/or recrystallization; furthermore, it may optionally be transformed to an acid addition salt, which in turn can be purified by recrystallization, if desired, after separation.

The compounds of the general formula (I) according to the invention, which contain a sufficiently strong basic group, may b transform d to acid addition salts. This trans-

formation is carried out by dissolving th base in a suitable solvent and then portionwise adding the appropriate (corresponding) acid or a solution of the acid in a solvent under stirring. The product thus obtained is separated by filtration or crystallization following evaporation of th solvent and, if desired, purified e.g. by recrystallization. Any organic or inorganic acid, preferably a pharmaceutically acceptable acid, such as hydrochloric, sulfuric, fumaric or tartaric acid may be used as acid compounent. E.g. alcohols, esters, ethers and/or ketones may be used as solvents. The salt formation is carried out at a temperature range of 0 °C to 80 °C, preferably between 0 °C and 20 °C when using mineral acids and preferably between 50 °C and 80 °C when using organic acids.

The compounds of general formula (I), wherein th meaning of $R^1$ and/or $R^2$ is hydrogen, can exist in (an) additional tautomeric form(s). These compounds are also within the scope of the invention.

The compounds of the general formula (I), wherein $R^3$ is different from hydrogen and/or the substituents $R^1$, $R^2$ and/or $R^4$ contain(s) (a) centre(s) of asymmetry, can exist also in optically active forms. The invention relates both to the racemates as well as to the optically active isomers.

A part of the compounds of general formula (II) used as starting substances in the process a) of the invention are known from the literature [see .g.: J. Am. Chem. Soc. 75, page 1909 (1953); Bull. Soc. Chim. France, page 2124 (1964); J. Heterocyclic Chem. 21, pag 481 (1984); Farmaco Ed. Sci.

32, page 780 (1977); ibid 40, page 921 (1985); Chem. Zvesti 38, page 239 (1984); and Chem. Pharm. Bull. 18, page 147 (1970)]; the compounds of general formula (II) not described thereto can analogously be prepared to methods known from the literature. E.g. the novel compounds of general formula (II) containing an alkenyl group substituted by an optionally substituted phenyl group, or an alkyl group substituted by a 4-substituted-1-piperazinyl group or a dimethoxybenzyl group as $R^1$ are prepared by reacting a 4,5-dihalo-3(2H)--pyridazinone with a suitable $R^1Y$ reagent, wherein Y stands for a leaving group, such as e.g. an $R^1$ halide compound. These methods will hereinafter be discussed in detail in the chapter "Preparation of the starting substances". An overwhelming majority of the $R^1Y$ reagents are known [see e.g.: J. Chem. Soc., page 1266 (1940); ibid., page 2516 (1961); J. Chem. Soc. B, page 590 (1966); J. Am. Chem. Soc. 83, page 3846 (1961); Chem. Ber. 30, page 810; Chem. Pharm. Bull. 25, page 1811 (1977)]; the new compounds can be prepared by methods described for or analogously to the preparation of known compounds.

A part of amino alcohols of the general formula (III) similarly used as starting substances in the process a) are also known from the literature [see e.g.: J. Am. Chem. Soc. 77, pages 633 and 636 (1955); Monatsh. 95, page 922 (1964); as well as the German patent specification No. 1,118,218]; the new compounds can be pr pared analogously to the compounds d scribed. Thus, 3-aminopropanols containing a 4--fluoro- or 3,4-dimethoxyb nzyl group as $R^2$ can be achieved

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by the in situ reduction with sodium borohydride of the Schiff's base obtained from the reaction of the resp ctive benzaldehyde with 3-amino-propanol; whereas 3-aminopropanol derivatives containing a benzyl group as $R^2$ and a 4--methoxyphenyl group as $R^4$ can be obtained by reducing the respective, known aminoketone prepared according to the literature [J. Am. Pharm. Assoc. Sci. Ed. 67, page 77 (1958)]. The preparation of 3-aminopropanols containing a 2--morpholinoethyl group as $R^2$ will be illustrated on th pre-paration of 3-[(2-morpholinoethyl)amino]propanol by reacting 2-morpholinoethyl chloride with 3-aminopropanol. These methods will hereinafter be discussed in detail in the chapter entitled "Preparation of starting substances".

The compounds of the general formula (I) according to the invention possess valuable biological effects, more particularly antianginal and calmodulin-antagonizing action.

The antianginal action of compounds according to the invention is supported by their advantageous effects exerted on the coronary blood flow and other characteristics (parameters) being important from the viewpoint of this action.

**I. Investigation of the coronary blood flow on anaesthetized open-chest dogs**

These examinations were carried out on mongrel dogs anaesthetized by 30 mg/kg of sodium pentobarbital (Nembutal$^R$) administered intravenously (i.v.).

The animals were artificially ventilated by a Harvard 612 A type r spirator of variabl phase through a trach al tube by performing a thoracotomy through the fifth inter-

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costal space. Subsequently, the pericardium was open d and the d scending branch of the l ft coronary artery (LAD) was exposed distally at 1.5 cm from its origin. An electromagnetic flow meter head was placed on the blood vessel which was joined to a Narcometic RT-500 type electromagnetic flow-measuring equipment. In this way the volume of the blood (ml/min) flowing through the exposed blood vessel section could be determined.

The myocardial contractile force (MCF) was measured by two methods. In a part of our experiments a strain gauge arch was placed on the epicardial surface of the left ventricle according to the method of Walton and Brodie [J. Pharm. Exp. Ther. 90, page 26 (1947)], whereas in other experiments a millar-tip catheter was introduced to the left ventricle, which made possible to measure the left ventricular pr ssur . The change in the tension of the strain gauge arch and the values obtained from the first derivative as a function of time (dP/dt) of the ascending branch of the left ventricular pressure wave, respectively, gave informations about th contractile state of the heart.

The systemic arterial blood pressure was determined by using a catheter inserted to the femoral artery and join d to a Statham P 23 Pb type pressure transducer and an electromanometer. The heart rate was also measured by using a cardiotachometer controlled by the pressure wave.

In order to determine the myocardial reactivity, 0.2 μg/kg of isoproterenol was intrav nously administered before giving the compounds under test. When given in this dose,

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isoproterenol as a beta-adrenergic stimulant exerts a temporary, reversibl eff ct increasing the myocardial contractile force and strengthening the coronary flow. In our experiments, isoproterenol was used for testing the myocardial reactivity of the experimental animals and not as a referenc drug.

In our experiments the change elicited by the compounds in the amplitude of the reactive hyperaemia (extreme increase in the coronary flow) following the occlusion of the descending branch of the left coronary artery for one minut was measured. The inhibition of the reactive hyperaemia indicates an advantageous effect of the compound under t st on the myocardial microcirculation.

The compounds under test were administered in the form of a bolus injection through the femoral vein.

The measurement characteristics (parameters) discussed above in detail were continuously registered on a Beckman 612 R type polygraph during the whole experimental period.

**II. Inhibition of the ST segment elevation induced by vasopressin on anaesthetized rats**

These investigations were carried out on male CFY rats with a body-weight of 200 to 250 g. After anaesthetizing the animals by 1 g/kg of intraperitoneally (i.p.) administered urethane, ECG records were taken up by using limb leads. Subsequently, a coronary spasm was induced by 3 IU/kg of vasopressin administered intravenously, which appeared as an elevation of the ST segment on the ECG r cord. Th eventual inhibition of the vasopressin-induced ST segment el vation by

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an intravenous pr tr atment of the animals with the compounds according to th invention was inv stigated. The inhibition proves the abolishment of hypoxia, an antianginal effect [J. Pharm. Methods 5, pages 325-336 (1981)].

Fendiline [chemically N-(3,3-diphenylpropyl)-N-(α-methylbenzyl)amine] and nicorandil [chemically N-(2-nitrooxyethyl)-3-pyridinecarboxamide] were used as reference drugs.

**Table I**

**Effect of compounds of the general formula (I) on th coronary resistance and vasopressin-induced ST segment elevation after i.v. administration**

| Compound (Example) No. | Change in coronary resistance (%) after 1 mg/kg dose | Inhibition of ST elevation after 5 mg/kg dose |
|---|---|---|
| 7 | -25.8 | -53 |
| 11 | -25.4 | -81 |
| 13 | -31.7 | -100 |
| 15 | -26.8 | -36 |
| 16 | -14.3 | -53 |
| 22 | -28.9 | -84 |
| 28 | -37.5 | |
| 32 | -38.5 | -72 |
| 34 | -25.8 | -20 |
| Nicorandil (reference drug) | -80.0 | -60 |
| Fendiline (reference drug) | -27.3 | -100 |

It is obvious from the data of Table 1 that the coronary resistance is significantly d creased and the

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vasopressin-induced ST segment elevation is significantly inhibited by the compounds of the invention, whereas these compounds have no significant influence either on the blood pressure or the heart rate and do not possess any negative inotropic effect; in addition, they inhibit the reactive hyperaemia. On this basis, the compounds of general formula (I) according to the invention are useful for the treatment of cardiovascular diseases, especially angina pectoris.

All those discussed above are supperted by the significant calmodulin-antagonizing effect of the compounds, which was determined as follows.

**Determination of the calmodulin-antagonizing effect**

For measuring the baseline activity of phosphodiesterase enzyme I [prepared as described in: Methods in Enzymology 102, page 39 (1983)], which can be activated by calcium-calmodulin, 0.9 ml volume of the reaction mixture contained 40 mmol of Tris, 40 mmol of imidazole, 5 mmol of magnesium acetate, 1.2 mmol of cyclic adenosine monophosphate (cAMP), alkaline phosphotase and phosphodiesterase enzym I in a buffer solution of pH 7.5. On determination of the enzyme activated by calcium-calmodulin, the above reaction mixture contained also 100 μmol of calcium chloride and 5.7 x x $10^{-9}$ mol of calmodulin. The enzyme reaction was arrested by adding 0.1 ml of 55 % trichloroacetic acid after incubation for 30 miutes and after centrifuging, the amount of inorganic phosphate formed was determined in the supernatant according to a method known from the literature [Anal. Biochem. 135, page 233 (1983)]. The $IC_{50}$ values were determined from the

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r gression curve of log concentration/% inhibition, based on th results of two parallel sampl s measured in five various concentrations. The results are summarized in Table 2.

**Table 2**

**Calmodulin-antagonizing effect of compounds of the g n ral formula (I)**

| Compound (Example) No. | $IC_{50}$ ($\mu M$) |
|---|---|
| 7 | 5.2 |
| 13 | 5.5 |
| 15 | 3.7 |
| 33 | 3.1 |
| Fendiline (reference drug) | 5.6 |

Based on the above data, the compounds of general formula (I) according to the invention possess a significant calmodulin-antagonizing effect and therefore, these compounds can be expected to have a very advantageous therapeutical use, particularly as antianginal agents on the basis of this inhibitory action, too.

The toxicity of these compounds is usually low. All these properties provide a valuable specftrum of effects as well as a therapeutic safety. For therapeutical use, a daily dos of the activ agents according to the invention is usually in th range of about 0.2 mg/kg of body-weight up to about 10 mg/kg of body-weight, optionally administered in

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divid d daily doses by considering also the conditions of resorption.

For therapeutical use, the active compounds of the invention are suitably formulated to pharmaceutical compositions by mixing them with non-toxic, inert, solid or liquid carriers and/or additives which are appropriate for enteral or parenteral administration and are commonly used in the therapeutical industry. E.g. water, gelatin, lactose, starch, pectin, magnesium starate, stearic acid, talc and vegetable oils are suitable carriers. As additives preserving, wetting (surface active), emulsifying or dispersing, buffering and aromatizing agents may be used.

By using the above carriers and additives, the aciv substances of the invention may be formulated to the usual pharmaceutical compositions, e.g. solid forms (such as tablets, capsules, pills and suppositories) or liquid forms (such as aqueous or oily solutions, suspensions, emulsions, syrups) as well as to injectable solutions, suspensions and emulsions.

The invention also relates to a method for treating heart or circulation (cardiovascular) diseases, particularly angina pectoris. This process comprises administering a therapeutically effective amount of an active ingredient of the general formula (I) to the patient.

The invention is illustrated in detail by the aid of the following non-limiting Examples.

Th compounds of general formula (I) given as examles, their (uncorrected) melting points or $R_f$ values, respective-

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ly of oils as well as th yield and m thod of preparation are given in the Examples and in Tables 3 and 4.

**Example 1**

**Preparation of 5-chloro-4-[N-(2-hydroxyethyl)-N-m thylamino]-2-(3-phenyl-2-propen-1-yl)-3(2H)-pyridazinone (method $A_1$)**

A solution containing 2.81 g (0.01 mol) of 4,5--dichloro-2-(3-phenyl-2-propen-1-yl)-3(2H)-pyridazinone [described hereinafter in the chapter entitled "Preparation of starting substances" method $a_1$)] and 2.25 g (0.03 m l) of 2-(N-methylamino)ethanol in 30 ml of anhydrous dioxane was boiled under reflux while stirring for 45 hours. After evaporating the solvent under reduced pressure, 30 ml of wat r were added to the residue and the pH value of the emulsion formed was adjusted to 7 by adding 10 % aqueous hydrochloric acid. After extracting the aqueous solution with ethyl acetate, the organic phase was dried and then evaporated. Th residue was subjected to column chromatography on silica gel by using chloroform/ethyl acetate mixtures with increasing polarity as eluent. The fractions showing an $R_f$ value of 0.56 (ethyl acetate) were combined to give the title compound in a yield of 1.00 g (34 %).

**Example 2**

**Preparation of 5-chloro-4-[(3-hydroxypropyl)amino]-2--(3-phenyl-2-propen-1-yl)-3(2H)-pyridazinone (method $A_2$)**

The above method $A_1$) was followed by using 4.00 g (0.014 mol) of 4,5-dichloro-2-(3-phenyl-2-propen-1-yl)-3(2H)-

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pyridazinon and 3.20 g (0.042 mol) of 3-aminopropanol, exc pt that n-butanol was used instead of dioxane and the reaction lasted for 10 hours to obtain 2.12 g (47 %) of the title compound, m.p.: 95-96 °C

**Example 3**

**Preparation of 2-allyl-4-[N-benzyl-N-(3-hydroxypropyl)amino]-5-chloro-3(2H)-pyridazinone (method $A_3$)**

The mixture of 3.33 g (0.01 mol) of 2-allyl-4,5--dichloro-3(2H)-pyridazinone with 6.61 g (0.04 mol) of 3-(N--benzylamino)propanol was stirred at 130 °C for 90 minutes. After cooling down, 40 ml of water were added to the reaction mixture, the pH was adjusted to 7 and the solution was extracted with ethyl acetate. After drying and evaporation, the crude product was purified according to method $A_2$ to obtain 0.66 g (20 %) of title product, $R_f$ = 0.62 (by developing with an 1:1 mixture of chloroform/ethyl acetate on silica gel).

**Example 4**

**Preparation of 2-benzyl-4-[N-benzyl-N-(3-hydroxypropyl)amino]-5-chloro-3(2H)-pyridazinone (method $A_4$)**

Method $A_1$ was followed by using 2.55 g (0.01 mol) of 2--benzyl-4,5-dichloro-3(2H)-pyridazinone and 24.78 g (0.15 mol) of 3-(N-benzylamino)propanol, except that toluene was employed instead of dioxane and the reaction lasted for 24 hours. In this way 1.53 g (40 %) of title product were obtained, $R_f$ = 0.33 (by developing with a 9:1 mixture of

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toluene/methanol on silica gel).

**Exampl 5**

**Preparation of 4-{N-benzyl-N-[3-hydroxy-1-(-methoxy-phenyl)]amino}-5-chloro-2-(3-phenyl-2-propen-1-yl)--3(2H)-pyridazinone (method $A_5$)**

Method $A_1$ was followed by using 3.10 g (0.011 mol) of 4,5-dichloro-2-(3-phenyl-2-propen-1-yl)-3(2H)-pyridazinon and 7.50 g (0.028 mol) of 3-(N-benzylamino)-1-(4-methoxy-phenyl)propanol, except that water was employed instead of dioxane to yield 0.65 g (11 %) of title product, $R_f$ = 0.44 (by developing with a 9:1 mixture of toluene/methanol on silica gel).

The compounds of Examples 6 to 30 were prepared by using the suitable starting substances and following methods $A_1$ to $A_5$. These compounds are summarized in Table 3.

**Example 31**

**Preparation of 4-{N-[3-(benzyloxy)propyl]-amino}--5-chloro-2-(3-phenyl-2-propen-1-yl)-3(2H)-pyridazin n (method B)**

0.23 g (1.7 mmol) of benzoyl chloride was dropwise added to a solution of 0.50 g (1.5 mmol) of 5-chloro-4-[N-(3--hydroxypropyl)amino]-2-(3-phenyl-2-propen-1-yl)-3(2H)--pyridazinone in 5 ml of pyridine at 10 °C under stirring and cooling by ice. The reaction mixture was stirred at 50 °C for 6 hours and then poured into 20 ml of ice-water. The solution was extracted with ethyl acetate and after washing the organic phase with 4 % hydrochloric acid and then with wat r, the organic phase was dried and evaporated. The evaporation

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residue was crystalliz d with ether to obtain 0.46 g (73 %) of title product, m.p.: 77-78 °C.

The compounds of Examples 32 and 33 were prepared from the suitable starting substances by using method B. The compound of Example 33 was purified by column chromatography. These compounds are summarized in Table 4.

**Example 34**

**Preparation of 4-[N-(3-acetyloxypropyl)-N-benzyl--amino]-5-chloro-2-(3-phenyl-2-propen-1-yl)-3(2H)--pyridazinone**

Method B was followed by using 0.61 g (1.5 mmol) of the compound of Example 13 and 0.35 g (3.4 mmol) of acetic anhydride to obtain 0.65 g (97 %) of title product, $R_f$ = = 0.88 (by developing with an 1:1 mixture of chloroform/ thyl acetate on silica gel).

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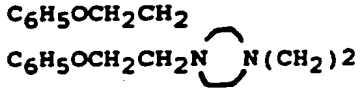
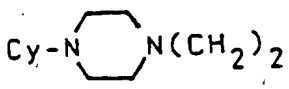
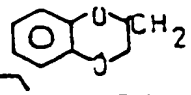
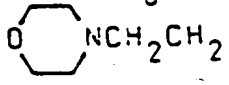
Tabl 3

| Example No. | $R^1$ | $R^2$ | $R^3$ | X | n | M.p. (°C) or $R_f$ | Yield (%) | Metho |
|---|---|---|---|---|---|---|---|---|
| 6 | $Et_2NCH_2CH_2$ | $CH_3$ | H | Cl | 1 | $0.50^5$ | 50 | $A_1$ |
| 7 | Cy | $C_6H_5CH_2$ | H | Cl | 1 | $0.62^2$ | 12 | $A_1$ |
| 8 | $CH_3$ | $C_6H_5CH_2$ | H | Cl | 2 | $0.40^2$ | 28 | $A_2$ |
| 9 | $HC\equiv C-CH_2$ | $C_6H_5CH_2$ | H | Cl | 2 | $0.26^2$ | 6 | $A_1$ |
| 10 | $C_6H_5$ | $C_6H_5CH_2$ | H | Cl | 2 | $0.60^2$ | 16 | $A_2$ |
| 11 | $4\text{-}CH_3O\text{-}C_6H_4CH_2$ | $C_6H_5CH_2$ | H | Cl | 2 | $0.48^2$ | 13 | $A_3$ |
| 12 | $3,4\text{-}(MeO)_2C_6H_3CH_2$ | $C_6H_5CH_2$ | H | Cl | 2 | $0.39^2$ | 21 | $A_2$ |
| 13 | Cy | $C_6H_5CH_2$ | H | Cl | 2 | 83-84 | 49 | $A_4$ |
| 14 | 4-MeO-Cy | $C_6H_5CH_2$ | H | Cl | 2 | $0.30^3$ | 22 | $A_3$ |
| 15 | 4-F-Cy | $C_6H_5CH_2$ | H | Cl | 2 | $0.34^3$ | 19 | $A_3$ |
| 16 | $C_6H_5CH_2OCH_2$ | $C_6H_5CH_2$ | H | Cl | 2 | $0.29^3$ | 5 | $A_1$ |
| 17 | $C_6H_5OCH_2CH_2$ | $C_6H_5CH_2$ | H | Cl | 2 | $0.44^2$ | 17 | $A_2$ |
| 18 |  | $C_6H_5CH_2$ | H | Cl | 2 | $0.40^4$ | 14 | $A_2$ |
| 19 |  | $C_6H_5CH_2$ | H | Cl | 2 | $0.33^4$ | 8 | $A_2$ |
| 20 | Cy | $4\text{-}MeO\text{-}C_6H_4CH_2$ | H | Cl | 2 | $0.54^2$ | 22 | $A_2$ |
| 21 | Cy | $4\text{-}F\text{-}C_6H_4CH_2$ | H | Cl | 2 | $0.77^2$ | 27 | $A_2$ |
| 22 | Cy |  | H | Cl | 2 | $0.39^2$ | 24 | $A_3$ |
| 23 | Cy |  | H | Cl | 2 | $0.64^2$ | 36 | $A_1$ |

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Tabl 3 (contd.)

| Example No. | $R^1$ | $R^2$ | $R^3$ | X | n | M.p. (°C) or $R_f$ | Yield (%) | M thod |
|---|---|---|---|---|---|---|---|---|
| 24 | $CH_3$ | $C_6H_5CH_2$ | H | Cl | 3 | 65-70 | 11 | $A_5$ |
| 25 | Cy | $C_6H_5CH_2$ | H | Cl | 3 | $0.24^7$ | 24 | $A_5$ |
| 26 |  | $C_6H_5CH_2$ | H | Cl | 3 | $0.28^6$ | 25 | $A_5$ |
| 27 | Cy | $C_6H_5CH_2$ | H | Br | 2 | 82-86 | 20 | $A_3$ |
| 28 | 4-OH-Cy | $C_6H_5CH_2$ | H | Cl | 2 | 128-131 | 16 | $A_4$ |
| 29 | H | $C_6H_5CH_2$ | H | Cl | 2 | 64-65 | 22 | $A_4$ |
| 30 | Cy | 3-pyridylmethyl | H | Cl | 2 | $0.69^5$ | 17 | $A_3$ |

Note: The upper signs mean the following systems used for determination of $R_f$ values: 1: ethyl acetate; 2: chloroform/ethyl acetate = 1:1; 3: toluene/methanol = = 9:1; 4: ethyl acetate/methanol = 9:1; 5: ethyl acetate/methanol/$NEt_3$ = 9:0.5:0.5; 6: ethyl acetate/ethanol = 4:1; 7: methylene chloride/ethyl acetate = 95:5.

Cy: 3-phenyl-2-propen-1-yl group

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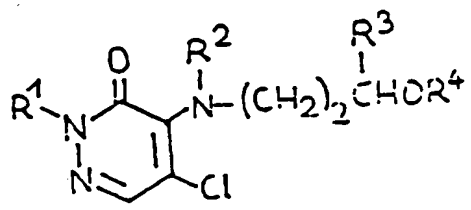
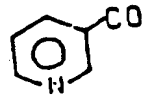
Tabl 4



| Example No. | $R^1$ | $R^2$ | $R^3$ | $R^4$ | X | M.p. (°C) or $R_f$ | Yield (%) | Metho |
|---|---|---|---|---|---|---|---|---|
| 32 | Cy | H | H |  | Cl | 81-82 | 68 | B |
| 33 | Cy | $C_6H_5CH_2$ | H | $(CH_3)_2CHCO$ | Cl | 0.80[2] | 9 | B |

**Example 35**

**Preparation of 4-{N-benzyl-N-[3-(butylcarbamoyloxy)-propyl]amino}-5-chloro-2-(3-phenyl-2-propen-1-yl)-3(2H)-pyridazinone**

After dropwise adding 0.60 g (6.06 mmol) of butyl isocyanate to 1.09 g (2.66 mmol) of the compound of Example 13 dissolved in 20 ml of benzene, the reaction mixture was boiled under reflux for 4 hours and then evaporated to dryness under reduced pressure. The residue was subjected to column chromatography on silica g l by using a solvent mixtur of chloroform and ethyl acetate to obtain 0.74 g (55 %) of title product, $R_f$ = 0.84 (by developing with an 1:1

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mixture of cloroform/ethyl acetate on silica gel).

**Exampl 36**

**Preparation of pyridinium-{3-[N-benzyl-N-[2-(3-phenyl--2-propen-1-yl)-5-chloro-3-oxo-4(2H)-pyridazinyl-amino]propyl}sulfate**

After portionwise adding 0.32 g (2 mmol) of pyridine-sulfur trioxide complex to the solution of 0.40 g (1 mol) of the compound of Example 13 in 4 ml of anhydrous pyridine below 10 °C under stirring and cooling by ice, the reaction mixture was stirred for 1 hour, then evaporated to dryness a 40 °C under a pressure of 1.33 x $10^2$ Pa and ether was twice distilled off from the oily residue. After taking up th residue in water and extracting with chloroform, the organic layer was washed with water and dried. The evaporation residue was suspended in ether, then petroleum ether, filtered and dried to give 0.45 g (80 %) of title product, m.p.: 102-103 °C.

**Example for the preparation of an acid additi n salt**

**Preparation of 5-chloro-2-(3-phenyl-2-propen-1-yl)-4--{3-[(3-pyridyl-carbonyloxy)propyl]amino}-3(2H)--pyridazinone hydrochloride**

The pH value of a solution containing 0.45 g (1 mmol) of the base of Example 32 in 5 ml of anhydrous ether was adjusted to 3 by adding 20 % ethanolic hydrogen chloride solution. After standing overnight at 5 °C, the crystalline pr cipitate was filtered, washed and dried to give 0.44 g (9 %) of title hydrochloride, m.p.: 115-119 °C.

**Preparation of 5-chloro-4-[N-(3-hydroxypropyl)-N-(2-morpholinoethyl)-amino]-2-(3-phenyl-2-propen-1-yl)-3(2H)-pyridazinone fumarate**

A solution of 0.40 g (3.5 mmol) of fumaric acid in 9 ml of ethanol was dropwise added to a solution containing 1.50 g (3.5 mmol) of the base of Example 23 in 9 ml of ethanol at 70 °C while stirring. After stirring at the same temperature for 10 minutes, the solution was evaporated to constant weight under reduced pressure to obtain 1.90 g (100 %) of the title fumarate.

**Preparation of starting substances**

1. **Examples for the preparation of novel 4,5-dihalo-3(2H)-pyridazinones of the general formula (II)**

**Method $a_1$): Preparation of 4,5-dichloro-2-(3-phenyl-2-propen-1-yl)-3(2H)-pyridazinone**

A solution of 16.8 g (0.11 mol) of cinnamyl chloride in 5 ml of anhydrous dimethylformamide was dropped to a suspension containing 16.5 g (0.10 mol) of 4,5-dichloro-3(2H)-pyridazinone and 150 g of anhydrous potassium carbonate in 100 ml of anhydrous dimethylformamide at a temperature below 15 °C under stirring. The reaction mixture was stirred at room temperature overnight and then poured into 600 ml of water while stirring. The crystalline precipitate was filtered, washed with water, dried and if necessary, purified by treatment with aluminum oxide in benzene solution. In this way 25 g (89 %) of the title compound were obtained, m.p.: 98-99 °C.

Further Examples using method $a_1$ are the compounds

listed hereinafter, which were prepared as described above by using the appropriate $R^1Cl$ compound instead of cinnamyl chloride:

4,5-Dichloro-2-[3-(4-fluorophenyl)-2-propen-1-yl]-3(2H)-pyridazinone, yield 59 %, m.p.: 124 °C.

4,5-Dichloro-2-[3-(4-methoxyphenyl)-2-propen-1-yl]-3(2H)-pyridazinone, yield 62 %, m.p.: 156-157 °C.

4,5-Dichloro-2-(2-phenoxyethyl)-3(2H)-pyridazinon , yield 98 %, m.p.: 94-97 °C.

4,5-Dichloro-2-(3,4-dimethoxybenzyl)-3(2H)-pyridazinone, yield 54 %, m.p.: 104-108 °C.

4,5-Dibromo-2-(3-phenyl-2-propen-1-yl)-3(2H)-pyridazinone (in this case 4,5-dibromo-3(2H)-pyridazinone was used instead of 4,5-dichloro-3(2H)-pyridazinone), yield 64 %, m.p.: 88-90 °C.

**Method $a_2$): Preparation of 4,5-dichloro-2-{2-[4-(2-phenoxyethyl)-1-piperazinyl]ethyl}-3(2H)-pyridazinone**

After portionwise adding 1.65 g (0.01 mol) of 4,5-dichloro-3(2H)-pyridazinone at room temperature to a solution prepared from 0.69 g (0.03 mol) of sodium in 20 ml of anhydrous ethanol under stirring, the stirring was continued for 15 minutes, then 3.41 g (0.01 mol) of 2-[4-(2-phenoxyethyl)-1-piperazinyl]ethyl chloride dihydrochloride were portionwise added. After boiling the reaction mixture under reflux and stirring for 2 hours, the precipitated sodium chloride was filtered and a salt was formed by adding

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ethanolic hydrogen chloride solution to the filtrate to obtain 3.43 g (73 %) of dihydrochloride of the title compound, m.p.: 208-210 °C.

Further Example using method $a_2$) is the compound named hereinafter, which was prepared as described above by using the appropriate $R^1Cl$ compound instead of 2-[4-(2-phenoxy-ethyl)-1-pyperazinyl]ethyl chloride dihydrochloride:

4,5-Dichloro-2-{2-[4-(3-phenyl-2-propen-1-yl)-1--piperazinyl]ethyl}-3(2H)-pyridazinone, yield 66 %, m.p.: 238-240 °C (dihydrochloride).

**Method $a_3$): Preparation of 4,5-dichloro-2-(4-m th xybenzyl)-3(2H)-pyridazinone**

After transforming 1.65 g (0.01 mol) of 4,5-dichloro--3(2H)-pyridazinone to its potassium salt by adding an equimolar amount of potassium hydroxide in methanol solution and then evaporating methanol under reduced pressure, the salt thus obtained was suspended in 30 ml of toluene, 1.56 g (0.0 mol) of 4-methoxybenzyl chloride dissolved in 30 ml of toluene were dropwise added under stirring, then 0.60 g (0.0018 mol) of tetrabutylammonium bromide was added. After boiling under reflux for 3 hours, the reaction mixture was evaporated to dryness under reduced pressure, the residue wa dissolved in water and the solution was extracted with ethyl acetate. After drying and evaporating, the crude product obtained was subjected to chromatography on silica gel by using ethyl acetate as luent to give 1.16 g (41 %) of title product, m.p.: 117-120 °C.

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**Method $a_4$): Preparation of 4,5-dichloro-2-[3-(4-hydroxyphenyl)-2-propen-1-yl]-3(2H)-pyridazinone**

To a solution containing 6.9 g (0.022 mol) of 4,5-dichloro-2-[3-(4-methoxyphenyl)-2-propen-1-yl]-3(2H)-pyridazinone in 130 ml of 98 % methanesulfonic acid, 30.4 g (0.20 mol) of methionine were portionwise added at room temperature under stirring. After the exothermic reaction, the mixture was maintained at 30 °C for 96 hours, then poured into 400 g of ice. The pH value of the solution was adjusted to 9 by adding concentrated ammonium hydroxide solution, the mixture was extracted with ethyl acetate and the organic phase was washed with water. After evaporation and drying, the oily residue was boiled under reflux with 92 ml of 2 N hydrochloric acid under stirring for 2 hours. After cooling down, the product was filtered, washed until neutral and dried. The crude product obtained was purified by chromatography on silica gel, using a 95:5 mixture of chloroform/ethyl acetate as eluent to yield 1.79 g (27 %) of title compound, m.p.: 193-195 °C.

**2. Examples for the preparation of novel 3-(substituted amino)propanols of the general formula (III)**

**Method $b_1$): Preparation of 3-[N-(4-fluorobenzyl)amino]-propanol hydrochloride**

7.60 g (0.10 mol) of 3-aminopropanol were dropped to a solution of 12.41 g (0.10 mol) of 4-fluorobenzaldehyd n 50 ml of ethanol below 10 °C. The solution was stirred at room temperature overnight and subsequently 3.80 g (0.10 mol) f sodium borohydride were portionwise added below 10 °C. The

reaction mixtur was stirred at the same temperature for 1 hour, at ro m temperatur overnight, then 10 ml of acetic acid were portionwise added below 10 °C and the mixture was stirred at room temperature for 1 hour. After filtering the reaction mixture, the filtrate was evaporated to dryness under reduced pressure and the residue was dissolved in 100 ml of 20 % sodium hydroxide solution. The solution was extracte with ethyl acetate and after drying, 20 % ethanolic hydrogen chloride solution was added at 5 °C to adjust the pH value t 3. The crystalline precipitate was filtered and washed with ether to obtain 19.1 g (87 %) of the title compound, m.p.: 136-137 °C.

Further Examples using method $b_1$) are the compounds listed hereinafter, which were prepared as described above b using the appropriate aldehyde instead of 4-fluorobenzaldehyde:

3-[N-(3,4-Dimethoxybenzyl)amino]propanol, yield 54 %, b.p.: 198-200 °C/266 Pa.

3-[N-(4-Methoxybenzyl)amino]propanol, yield 70 %, m.p.: 140-141 °C(HCl).

3-[N-(3-Pyridylmethyl)amino]propanol, yield 65 %, m.p.: 163-165 °C(HCl).

**Method $b_2$): Preparation of 3-(N-benzylamino)-1-(4--methoxyphenyl)-1-propanol**

To a solution containing 3.00 g (0.01 mol) of -(N--benzylamino)-4-methoxypropiophenone in 130 ml of methanol, 5.50 g (0.15 mol) of sodium borohydride were portionwise added below 20 °C under stirring, then the reaction mixture

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was stirred at room temperature for 1 hour. Subsequently, 10[illegible] ml of 5 % acetic acid were dropp d to the mixture, methanol was removed under reduced pressure, the residue was filtered and the filtrate was alkalinized by adding sodium carbonate. After extracting with ethyl acetate, the organic layer was washed with water, dried and evaporated. The residue was suspended in ether and after filtering, the crystals were dried to give 2.06 g (76 %) of the title compound, m.p.: 65-66 °C.

**Method $b_3$): Preparation of 3-[N-(2-morpholinoethyl)-amino]propanol**

A mixture of 9.30 g (0.05 mol) of 2-morpholinoethyl chloride hydrochloride with 15.0 g (0.20 mol) of 3-aminopropanol was stirred at 140 °C for 4 hours, then cooled to room temperature and 100 ml of water were added. After extracting with chloroform, the organic phase was dried, evaporated and the residue was distilled under reduced pressure to obtain 5.65 g (60 %) of the title compound, b.p.: 138-140 °C/200 Pa.

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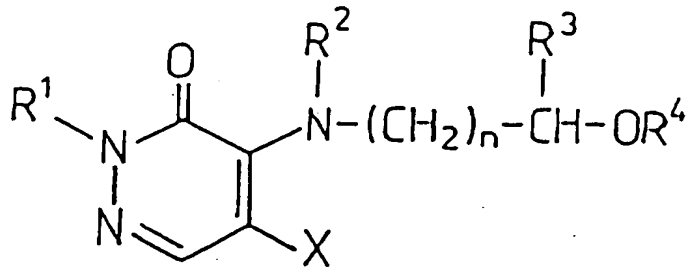
## Claims

1. Racemic and optically active 3(2H)-pyridazinone derivatives of the general formula (I)



(I

wherein

$R^1$ means hydrogen; a $C_{1-4}$alkyl group optionally substituted by an $R^5R^6N$- group where $R^5$ and $R^6$, being the same or different, stand for a $C_{1-4}$alkyl group or $R^5R^6N$- together represents a 6-membered heterocyclic group optionally containing an oxygen or an $R^7N$- moiety where $R^7$ is a $C_{1-4}$alkyl optionally substituted by a phenyoxy group or a $C_{3-5}$alkenyl optionally substituted by a phenyl grup; or a $C_{1-4}$alkyl group substituted by a mono- or polysubstituted phenyl, phenoxy or benzyloxy group; or a $C_{3-5}$alkenyl or $C_{3-5}$alkynyl optionally substituted by an unsubstituted or optionally substituted phenyl group; or a phenyl group;

$R^2$ means hydrogen; or a $C_{1-4}$alkyl optionally substituted by a morpholino, pyridyl, 1,4-benzodioxanyl or an optionally substituted phenyl group;

$R^3$ means hydrogen or an optionally substituted phenyl

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group;

$R^4$ means hydrogen; or $R^8CO$- group where $R^8$ is a $C_{1-4}$alkyl phenyl or pyridyl group or an amino group substituted by a $C_{1-4}$alkyl group; or an $-SO_3M$ moiety where M is hydrogen or an organic or inorganic cation;

X means halogen; and

n is 1, 2 or 3,

with the proviso that $R^1$ is different from a $C_{1-4}$alkyl, alkenyl, aralkyl and phenyl group when n is 1,

as well as their tautomers and the acid addition salts of these compounds.

2. A compound selected from the group consisting of 5-chloro-2-(3-phenyl-2-propen-1-yl)-4-{3-[(3-pyridylcarbonyloxy)propyl]amino}-3(2H)-pyridazinone,

4-[N-benzyl-N-(3-hydroxypropyl)amino]-5-chloro-2-(3-phenyl-2-propen-1-yl)-3(2H)-pyridazinone,

4-[N-benzyl-N-(3-hydroxypropyl)amino]-5-chloro-2-(4-methoxybenzyl)-3(2H)-pyridazinone

and the acid addition salts of these compounds.

3. A pharmaceutical composition, which comprises as active ingredient a ovel, racemic or optically active 3(2H)-pyridazinone derivative of the general formula (I), wherein $R^1$, $R^2$, $R^3$, $R^4$, X and n are as defined in claim 1, or a tautomer thereof or a pharmaceutically acceptable acid addition salt thereof as defined in claim 1, in admixture with carriers and/or additives commonly used in the pharmaceutical industry.

4. A process for the preparation of the novel 3(2H)-

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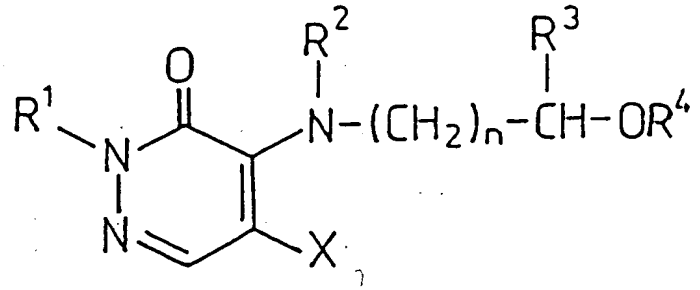
-pyridazinone dervatives of general formula (I)



(I

wherein

$R^1$ means hydrogen; a $C_{1-4}$alkyl group optionally substituted by an $R^5R^6N$- group where $R^5$ and $R^6$, being the same or different, stand for a $C_{1-4}$alkyl group or $R^5R^6N$- together represents a 6-membered heterocyclic group optionally containing an oxygen or an $R^7N$- moiet where $R^7$ is a $C_{1-4}$alkyl optionally substituted by a phenyoxy group or a $C_{3-5}$alkenyl optionally substituted by a phenyl grup; or a $C_{1-4}$alkyl group substituted by mono- or polysubstituted phenyl, phenoxy or benzyloxy group; or a $C_{3-5}$alkenyl or $C_{3-5}$alkynyl optionally substituted by an unsubstituted or optionally substituted phenyl group; or a phenyl group;

$R^2$ means hydrogen; or a $C_{1-4}$alkyl optionally substituted by a morpholino, pyridyl, 1,4-benzodioxanyl or an optionally substituted phenyl group;

$R^3$ means hydrogen or an optionally substituted phenyl group;

$R^4$ m ans hydrogen; or $R^8CO$- group where $R^8$ is a $C_{1-4}$alkyl, phenyl or pyridyl group or an amino group substituted

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by a $C_{1-4}$alkyl group; or an $-SO_3M$ moiety where M is hydrogen r an organic or inorganic cation;

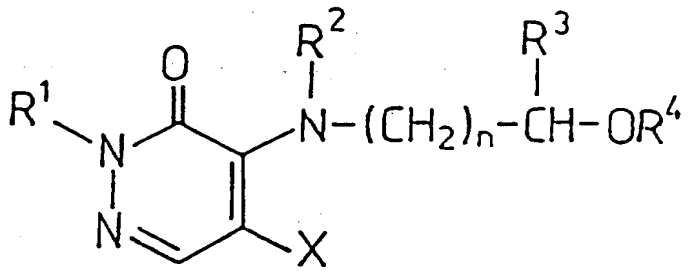
X means halogen; and

n is 1, 2 or 3,

with the proviso that $R^1$ is different from a $C_{1-4}$alkyl, alkenyl, aralkyl and phenyl group when n is 1,

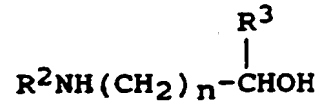
as well as their tautomers, racemic and optically active forms, mixtures thereof and acid addition salts of these compounds, which comprises

a) reacting a compound of general formula (II),



(II

wherein $R^1$ and X are as defined above, with an amine o the general formula (III),



(III

wherein $R^2$, $R^3$ and n are as defined above,

to obtain compounds of the general formula (I), wherei $R^4$ stands for hydrogen and $R^1$, $R^2$, $R^3$, X and n are as defin d above; or

b) treating a compound of the general formula (I), wherein $R^4$ means hydrogen, $R^1$ is as defined above,

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except hydrog n, and $R^2$, $R^3$, X as well as n are as defined above, with an agent being suitable to introduce an $R^8CO$- group, where $R^8$ is as defined above to obtain compounds of the general formula (I), wherei $R^4$ stands for $R^8CO$- group, $R^1$ is as defined above, except hydrogen, and $R^2$, $R^3$, X, n and $R^8$ are as define above; or

c) treating a compound of the general formula (I), wherei $R^4$ means hydrogen, $R^1$ is as defined above, except hydrogen, and $R^2$, $R^3$, X and n are as defined above, with chlorosulfonic acid or with a complex of sulfur trioxide being suitable to introduce the sulfonic acid group, then, if desired, transforming the compound thu obtained to its salt by reacting it with an organic or inorganic base,

to obtain compounds of the general formula (I), wherei $R^4$ represents an $-SO_3M$ group, $R^1$ is as defined above, except hydrogen and $R^2$, $R^3$, X, n and M are as defined above,

and, if desired, transforming a base of the general formula (I), wherein $R^1$, $R^2$, $R^3$, $R^4$, X and n are as defined above, obtained by any of the above processes a) to c), to its acid addition salt in a manner known per se and/or, if desired, transforming one of its acid addition salts to an other acid addition salt and/or, if desired, liberating a base of the general formula (I) from its salt.

5. A process as claimed in process b) of claim 4, whic comprises using as an active carboxylic acid derivative and

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optionally an acid binding agent, or an alkyl isocyanate as an agent being suitable to introduce an $R^8CO$- group.

6. A process as claimed in claim 5, which comprises using an acyl chloride or acid anhydride as reactive carboxylic acid derivative and a tertiary amine as acid binding agent.

7. A procss for the preparation of a pharmaceutical composition, which comprises mixing as active ingredient a novel racemic or optically active 3(2H)-pyridazinone derivative of the general formula (I), wherein $R^1$, $R^2$, $R^3$, $R^4$, X and n are as defined in claim 1, or a tautomer thereof or a pharmaceutically acceptable acid addition salt thereof as defined in claim 1, prepared by using process a), b) or c) claimed in claim 4, with carriers and/or additives commonly used in the pharmaceutical industry and transforming them tc a pharmaceutical composition.

8. Method for treating mammals (including man) suffering from angina pectoris, which comprises administerin a therapeutically effective amount of a novel, racemic or optically active 3(2H)-pyridazinone derivative of the general formula (I), wherein $R^1$, $R^2$, $R^3$, $R^4$, X and n are as defined in claim 1, or a tautomer thereof or a pharmaceutically acceptable acid addition salt thereof as defined in claim 1, to a subject in need of such treatment.

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# INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 91/00054

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.[5]: C 07 D 237/22; A 61 K 31/50

## II. FIELDS SEARCHED

Minimum Documentation Searched [7]

| Classification System | Classification Symbols |
|---|---|
| Int.Cl.[5] | C 07 D 237/00; A 61 K 31/00 |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

| Category [10] | Citation of Document, [11] with indication, where appropriate, of the relevant passages [12] | Relevant to Claim No. [13] |
|---|---|---|
| D,A | CS, B1, 223 432 (KONECNY et al.) 15 March 1986 (15.03.86), see claims. | 1,4 |
| A | EP, A1, 0 400 519 (THOMAE) 05 December 1990 (05.12.90), see claims 1,3,7,10. | 1,3,4 |
| A | US, A, 4 666 902 (ZOLLER et al.) 19 May 1987 (19.05.87), see abstract. | 1,3 |

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 18 March 1992 (18.03.92) | 01 April 1992 (01.04.92) |
| **International Searching Authority** | **Signature of Authorized Officer** |
| AUSTRIAN PATENT OFFICE | Veinsberg Hueber |



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FURTHER INF RMATION CONTINUED FROM THE SEC ND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 8 because they relate to subject matter not required to be searched by this Authority, namely:

See PCT, Rule 39.1(iv) Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers ..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers ....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.



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# ANHANG

zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

# ANNEX

to the International Search Report to the International Patent Application No.

# ANNEXE

au rapport de recherche international relatif à la demande de brevet international n°

PCT/HU 91/00054

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The Office is in no way liable for these particulars which are given merely for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsibilité de l'Office.

| Im Recherchenbericht angeführtes Patentdokument<br>Patent document cited in search report<br>Document de brevet cité dans le rapport de recherche | Datum der Veröffentlichung<br>Publication date<br>Date de publication | Mitglied(er) der Patentfamilie<br>Patent family member(s)<br>Membre(s) de la famille de brevets | Datum der Veröffentlichung<br>Publication date<br>Date de publication |
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